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Review article

The effect of mind-body and aerobic exercise on negative symptoms in schizophrenia: A meta-analysis

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ABSTRACT

Objective: This meta-analysis aims to evaluate the effects of different types of physical exercise (PE) on negative symptoms in schizophrenia patients. Mind-body exercise (MBE), aerobic exercise (AE) and resistance training (RT) will be investigated.
Method: The Cochrane Library, Medline, Embase and PsycINFO were searched from their inception until April 26, 2018. Randomized controlled trials comparing PE with any control group in patients with schizophrenia were included when negative symptoms had been assessed. This meta-analysis was conducted according to the PRISMA guidelines. The methodological quality of the included studies was assessed with the Cochrane Risk of Bias assessment tool. Moderator, sensitivity, and meta regression analyses were conducted to explore causes of heterogeneity and impact of study quality.
Results: We included 22 studies ($N = 1249$). The overall methodological quality was poor. The meta-analysis (random effects model) showed a medium significant effect in favor of any PE intervention (Hedges' $g = 0.434$, 95% CI = 0.196–0.671) versus any control condition. MBE and AE respectively showed a medium significant effect (Hedges' $g = 0.461$) and a small significant effect (Hedges' $g = 0.341$) versus any control condition. The effect of RT could not be examined. The overall heterogeneity was high ($I^2 = 76\%$) and could not be reduced with moderator or sensitivity analyses.
Conclusion: This meta-analysis demonstrated that PE could be a promising intervention in the treatment of negative symptoms. However, the quality of the included studies was low and heterogeneity was high, which makes it impossible to make a clear recommendation. Therefore, results should be interpreted with care.

1. Introduction

Negative symptoms in patients with schizophrenia are strongly associated with increased disease burden and problematic social outcome, such as a smaller social network and lower social functioning (Degnan et al., 2018; Mäkinen et al., 2008; Rocca et al., 2014). Negative symptoms are present in 50–90% of the patients with a first episode psychosis (FEP) and persisting negative symptoms are found in 20–40% of the patients with schizophrenia (Mäkinen et al., 2008). These symptoms are associated with low psychosocial functioning, such as vocational/academic and self-care problems (Stouten et al., 2014). Negative symptoms are a predictor of poor functional recovery at 12 months (Alvarez-Jimenez et al., 2012) and 7,5 years (Ventura et al., 2015) after FEP. This profound impact on patients' lives warrants the research on effective treatments of negative symptoms (Kirkpatrick et al., 2006).

Several different interventions targeting negative symptoms in schizophrenia have been investigated in previous research. Psychological and pharmacological interventions did not lead to clinically relevant improvements (Fusar-Poli et al., 2014) and the evidence on Cognitive Behavioral Therapy (CBT) (Aleman et al., 2017; Lutgens et al., 2017; Velthorst et al., 2014) and Transcranial Magnetic

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Stimulation (TMS) is inconclusive (Aleman et al., 2018; Dougall et al., 2015; Shi et al., 2014).

Negative symptoms are associated with impairments in effort-cost computations (Gold et al., 2013), meaning that people with schizophrenia presumably overestimate costs and underestimate reward of possible pleasurable behaviors. This in turn results into clinical manifestations of negatives symptoms, such as amotivation and apathy (Ferveha et al., 2013). This effort-based decision paradigm might be the putative mechanism in understanding the effect of physical exercise (PE) for negative symptoms. PE is generally perceived as a high effort activity, but with beneficial effects in neural pathways for reward (Herrera et al., 2016; Bothe et al., 2013). Therefore, repetitive training in PE might have positive effects on effect-cost computations in schizophrenia and subsequently in negative symptoms. Aside from an effect on negative symptoms, previous studies have also shown beneficial effects of PE on working memory, social cognition, attention/vigilance (Firth et al., 2017; Lin, 2014), cardiorespiratory fitness (Vancampfort et al., 2015) depression and PANSS scores (Lin, 2014; Vera-Garcia et al., 2015) in schizophrenia. This accumulation of beneficial effects makes PE an exceptionally interesting intervention for people with a psychotic disorder.

Previous reviews and meta-analyses have demonstrated that different types of PE interventions, such as aerobic exercise (AE) (Firth et al., 2015), yoga (Broderick et al., 2015, 2017), and tai chi (Zheng et al., 2016), resulted in significant effects on negative symptoms in schizophrenia. In recent years, new intervention studies were published on these different types of PE that have not been included in any previous reviews (Bhatia et al., 2017; Kang et al., 2016; Loh et al., 2015; Su et al., 2016; Svatkova et al., 2015). An update of the evidence of PE on negative symptoms is therefore needed. Furthermore, most previous reviews and meta-analyses have evaluated the effects of a specific type of PE interventions on negative symptoms. To our knowledge, only one previous meta-analysis by Dauwan et al. (2015) has evaluated the combined subtypes of PE in people with schizophrenia. An important difference of their meta-analysis compared to this meta-analysis is that it included uncontrolled studies, which might have weakened the strength of the evidence. The current meta-analysis will update the existing knowledge on the effects of PE on negative symptoms by including the most recent studies and will only include randomized controlled trials (RCT) to provide the strongest evidence. Furthermore, this meta-analysis will make a distinction between mind-body exercise (MBE), aerobic exercise (AE) and resistance training (RT) and aims to determine the effect of these different types of PE compared to active control and treatment as usual (TAU) groups.

1.1. Aim of the study

This meta-analysis aims to investigate the overall effects of physical exercise interventions that focus on relaxation and on exertion (including mind-body exercise, aerobic exercise and resistance training) in reducing negative symptoms in schizophrenia.

2. Material and methods

This meta-analysis was conducted in accordance with the PRISMA guidelines for systematic reviews and meta-analyses. The protocol (accession number CRD42018073983), including the search strategy, is electronically accessible through Prospero (Centre for Reviews and Dissemination).

2.1. Study identification and inclusion

All RCTs measuring the effect of PE on negative symptoms in schizophrenia were eligible for inclusion when patients were diagnosed with schizophrenia or schizophrenia related disorders (as defined by the DSM IV and V American Psychiatric Association, 2000, 2013 or ICD World Health Organization, 2016), aged 18 years or older, treated in all settings (e.g. inpatient and outpatient) as well as all clinical stages. We only included studies which used standardized measurement instruments for negative symptoms, such as the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1988) and the Scale for Negative Symptoms Assessment (SANS) (Andreasen, 1989). PE was defined as "planned, structured, and repetitive with the purpose of improvement or maintenance of one or more components of physical fitness" (Caspersen et al., 1985). We included interventions that focus on relaxation and interventions that focus on exertion. The intervention or control group consisted of MBE, AE or RT. MBE integrates physical movements combined with an inner mental focus (e.g. tai chi or yoga). AE was subdivided in light aerobic exercise (light AE) and moderate aerobic exercise (moderate AE). Interventions were classified as light AE if the largest part of the exercise consisted of low energy expenditure activities such as walking. Interventions were classified as moderate AE if interventions consisted of high energy expenditure activities such as cycling or running (>5 min). Furthermore, we labeled interventions as moderate AE if they were described as such in the original article. RT is characterized by forcing skeletal muscles to contract, for example by weight lifting or using one's own weight (Plowman and Smith, 2007). RCT's with any control group (active and/or inactive control conditions) were eligible for inclusion. Interventions in the active control conditions are initiated within the RCT to control for non-specific intervention effects. Inactive control groups are groups that receive treatment as usual (TAU) or are assigned to a waiting list. No restrictions were held on frequency or duration of PE, nor on the utilities of the training or the therapist. Inclusion was limited to peer reviewed studies published in English.

2.2. Databases and selection process

The following databases have been searched until April 26, 2018: Cochrane's database of Controlled Clinical trials, Medline, Embase and PsycINFO. All databases were searched through OVID interface. The following search terms and their synonyms were used: schizophrenia, exercise, randomized controlled trial and therapy (for more detailed information see the supplementary file S1). Authors JSV and SC performed the selection of studies. Publications were selected independently by title and abstract. A kappa statistic was used to measure the inter-rater agreement with fair (>0.40), good (>0.60) or excellent agreement (>0.75) (Orwin, 1994). Full text articles were retrieved from the selected abstracts and these were screened for the inclusion criteria by JSV. A subset of 25% of all full text articles was independently screened for inclusion by SC. Discrepancies were discussed in a consensus meeting. Recent reviews and meta-analyses were screened for additional studies, not retrieved by the search. Formal testing of publication bias was done by Eggers' regression intercept (Egger et al., 1997) and Kendalls Tau (Begg and Mazumdar, 1994) (2 sided) with a significance level of $p < 0.05$. A significant outcome on one or both tests was followed by applying the Duval and Tweedie's Trim and Fill procedure (Duval and Tweedie, 2000).

2.3. Data extraction

The extracted data consisted of: aim of the study, number of patients included, population characteristics (age, gender, setting, and duration of illness), comparison of intervention and control groups, number of therapeutic sessions, supervision, group or individual delivery, duration of treatment, used outcome scales and reported effects (i.e. means and standard deviations). In case of missing outcome data, the corresponding author (and/or last author) of the study was contacted by email. Data extraction was performed by author JSV and verified by author CS and a research assistant of Lentis Psychiatric Institute independent from the study.

2.4. Assessment of risk of bias

Risk of bias (RoB) was assessed using the Cochrane RoB assessment tool (Higgins and Green, 2008). This measure comprises six areas of the trial design: sequence generation, allocation concealment, blinding of assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Items were rated as high risk, low risk or unclear risk of bias. The total score ranges from 1 to 6, with higher scores meaning less RoB. Authors JSV and JB rated the RoB score. A kappa score examined the scores of both assessors with fair, good or excellent agreement (Orwin, 1994). Discrepancies were solved in a consensus meeting.

2.5. Synthesis of the results

Comprehensive Meta-Analysis v3 (Borenstein et al., 2014) was used to examine the treatment effect of the PE interventions. Due to the heterogeneity of the offered treatments (e.g. duration, number of sessions, control conditions) and population (e.g. country of origin, disease severity) a random effects model was used. Heterogeneity was addressed with the I^2 statistic (range 1–100%: absent (0%), low (25%), moderate (50%) or high (75%)) and the Q statistic (substantial heterogeneity is present if $p < 0.05$) (Higgins et al., 2003). Hedges' g was used to measure the effect size as this measure corrects for small sample sizes. Intervention and control conditions in the overall analyses were pooled for studies with more than one intervention or control group in order to prevent double counting of subjects (Higgins and Green, 2008). All subtypes of PE were first analyzed together. Subsequently, in subgroup analyses the separate effects for MBE and AE were computed. AE was further subdivided into moderate AE and light AE. Sensitivity analyses were conducted to explore heterogeneity and the impact of control groups (i.e. active control and TAU groups). Moderator analyses were conducted on high quality studies having a clear description of blinding and ≥4 points on the Cochrane RoB tool. Other moderator analyses where performed on number of sessions (>36 sessions) and duration (>12 weeks), based on recommendations in a review of Stanton and Happell (2014). Also, in a meta regression analysis we evaluated the impact of the number of sessions and duration of the intervention (in weeks) on the outcome. A post hoc analysis was conducted to explore the impact of supervision on drop-out rates with the use of Pearson's correlation coefficient.

3. Results

3.1. Literature search

The search and inclusion process are presented in Fig. 1. The initial search resulted in 508 studies. Two studies had a second publication based on the same study sample (Behere et al., 2011; Paikkatt et al., 2012, 2015; Varambally et al., 2012). Only the most recent publication was considered eligible for inclusion. A good interrater agreement was found for the inclusion process ($\kappa = 0.60$). As we found only one study that evaluated the effect of RT, a consensus decision was made to exclude this study and to focus our further analyses on MBE and AE (Silva et al., 2015). Two more studies were excluded, because the article did not contain sufficient information about the intervention that was investigated (Kwon et al., 2006) or the authors did not respond to our request for more information (Gholipour et al., 2012). In total, 24 studies were included. Two studies only compared MBE to light AE (Manjunath et al., 2013; Duraiswamy et al., 2007). These studies were analyzed separately, leaving 22 studies in the main analysis comparing PE to active control and TAU groups.

3.2. Setting, participant and intervention characteristics

The majority of the patients ($N = 1249$) was male (58%) and outpatient (12 studies). The mean number of sessions was 33 (range: 8–104, with one study not reporting the number of sessions (Jayaram et al., 2013)) with a mean duration of 12 weeks (range: 3–52). An overview of the setting, intervention and patient characteristics are described in Table 1.

3.3. Risk of bias

Across studies the RoB for random sequence generation and blinding was sufficient in >70% of the studies. Allocation concealment, incomplete outcome data and other biases were sufficient in 50% of the studies. Two studies (8%) sufficiently reported selection bias. The RoB across studies is reported in Fig. 2 and summary scores of the RoB per study are reported in Table 1. Furthermore, the RoB per study at item level can be found in the supplementary file S2. The agreement between the assessors was moderate ($\kappa = 0.44$). Testing for publication bias revealed one missing study in the main analysis. The Duval and Tweedie's Trim and Fill procedure (Duval and Tweedie, 2000) showed that correction for publication bias was not needed (i.e. no unpublished negative studies were detected).

3.4. Outcomes

The overall meta-analysis ($N = 22$) showed a medium significant effect in favor of PE (Hedges' $g = 0.434$, 95% CI = 0.196, 0.671), but with high statistical heterogeneity ($I^2 = 76\%$, $Q = 75.6$ (df = 21), $p < 0.000$). MBE interventions showed a statistically significant effect size in a subgroup analysis (Hedges' $g = 0.461$, 95% CI = 0.131, 0.790), but with high heterogeneity ($I^2 = 81\%$, $Q = 57.9$ (df = 11), $p < 0.000$). AE showed a small significant effect of $g = 0.341$ (95% CI = 0.079, 0.604), with moderate to high heterogeneity ($I^2 = 64\%$, $Q = 36.0$ (df = 13), $p = 0.001$). Forest plots of the main analysis and the subgroup analyses are demonstrated in Fig. 3. Four studies evaluated the effect of MBE versus light AE. A meta-analysis on these studies did not result in a significant effect (Hedges' $g = 0.266$, 95% CI = −0.128, 0.659).

3.5. Sensitivity analyses

Sensitivity analyses were conducted for MBE in order to examine the origins of the high heterogeneity (see Table 2 for effect sizes and heterogeneity). Separating active control groups from TAU was not useful as only two studies compared MBE to active control groups. Also, other possible moderators such as low RoB, removing two outlier studies, number of sessions, outpatients, the use of a supervised intervention, or group versus individual treatment did not reduce heterogeneity.

Sensitivity analyses were also conducted for AE in order to examine the origins of the high heterogeneity (see Table 2 for effect sizes and heterogeneity). Heterogeneity could be removed to low by limiting the analysis to moderate AE ($k = 10$), but this reduced the effect size to a statistically non-significant Hedges' g of 0.24. Heterogeneity was absent in moderate AE versus active control ($k = 5$), but the effect size was then reduced to $g = -0.003$ (ns). With low RoB or more than 36 sessions the effect sizes reduced to statistically insignificant levels. The effect sizes remained significant with outliers removed ($g = 0.29$), outpatients ($g = 0.40$), group interventions ($g = 0.43$), but they are still heterogeneous. A meta regression analysis on the number of sessions and duration of the intervention (in weeks) did not show significant results. Only one moderator could remove the heterogeneity and that was the use of supervised interventions ($I^2 = 37$, $Q = 33.6$ (df = 10), $p = 0.11$) (Hedges' $g = 0.24$, 95% CI = 0.010–0.478).

3.6. Post hoc analyses

A post hoc analysis was conducted on the correlation between

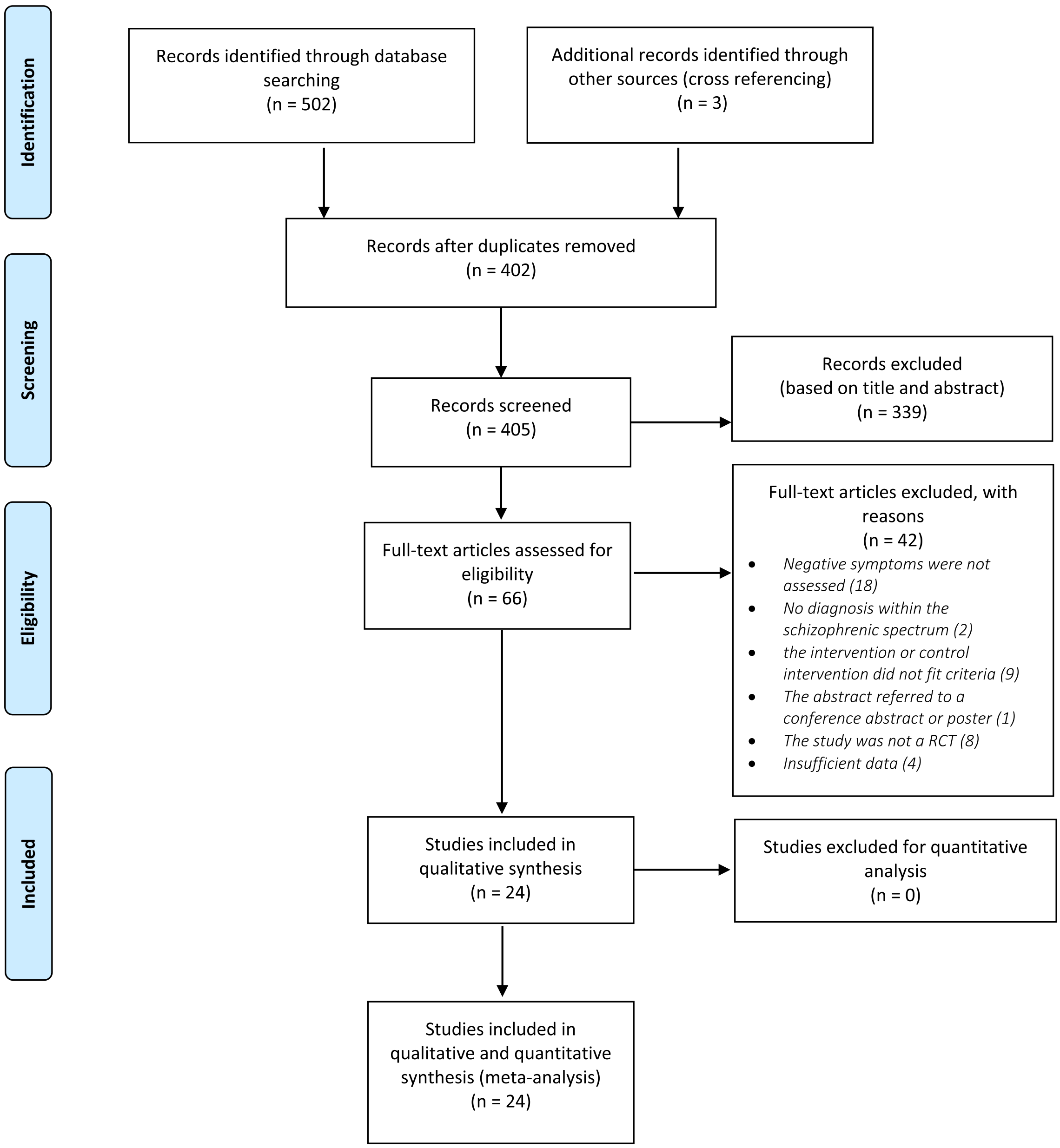

Fig. 1. Flow diagram of included studies.

supervised interventions and drop-outs. This correlation was non-significant.

4. Discussion

4.1. Summary of main findings

Overall, PE interventions were only effective in comparison with TAU, but not when compared to active control groups (e.g. occupational therapy or token reinforcement). The intervention effects might not be attributable to PE specifically, but are rather a general effect of interventions that appeal on activation, as is seen in the active control groups (Lutgens et al., 2017). This could explain the absence of an effect in meta-analyses with PE interventions versus active control groups. The subgroup analysis of mind-body exercise (MBE) showed promising results in treating negative symptoms in schizophrenia. We found a moderate effect size for MBE, but the statistical heterogeneity was high and could not be reduced in sensitivity analyses. Therefore, we were not able to identify which active components of mind-body interventions are essential for its effectiveness on negative symptoms. This could be explained by the variety of interventions that were included. Different types of MBE (e.g. chair yoga, hatha yoga and tai chi) might have different effects on negative symptoms in schizophrenia. Similarly, there was a small to medium effect of AE on negative symptoms, with moderate heterogeneity among the studies. The heterogeneity was reduced to small including only interventions with a supervisor. Furthermore, a considerable RoB was present across studies. Analyzing only high-quality studies did not change the significant effect of MBE interventions on negative symptoms, but the effects of AE interventions became non-significant.

4.2. Agreements and disagreements with previous research

In recent years six meta-analyses on exercise have been published (Broderick et al., 2015, 2017; Dauwan et al., 2015; Firth et al., 2015; Lutgens et al., 2017; Zheng et al., 2016), but the comparability is limited as different statistical analyses were used to analyze the PANSS and SANS data. For example, the reviews of Dauwan et al. (2015), Firth

Table 1
Description of included studies: the country, setting, outcome scale, intervention and patient characteristics, attrition and risk of bias.

Study	Country	Setting	Outcome Scale	Format	Intervention descriptions	Treatment delivery	No. of sessions (duration in weeks)	duration (weeks)	N	Mean age (SD)	Duration of illness (years)	Intervention drop-outs	RoB
Acil (2008)	Turkey	Outpatient	SANS	Moderate AE	Limber up figures (10 min); aerobic exercises (25 min); cool down figures (5 min)	Group	30 (10)	10	15	32.1 (N/A)	10.3	0	0
				TAU	Treatment as usual				15	32.7 (N/A)		0	
Beebe (2005)	United States	Outpatient	PANSS-N	Light AE	Warm-up stretches (10 min); treadmill walking (30 min) cool down stretches (10 min)	Group	48 (16)	16	6	52.0 (N/A)	8.6	2	3
				TAU	Treatment as usual				6			0	
Bhatia (2017)	India	Outpatient	SANS	MBE	Yoga postures; breathing; nasal cleansing	Group	21 (3)	3	104	34.8 (9.6)	N/A	18	4
				Light AE	Brisk walking (10 min); jogging (5 min); exercises in standing; sitting postures (20 min)				90	35.2 (9.5)		15	
				TAU	Treatment as usual				92	35.7 (10.1)		15	
Duraiswamy (2007)	India	Inpatient and outpatient	PANSS-N	MBE	Loosening exercises (10 min); yoga postures (20 min); breathing exercises (18 min); relaxation (3 min)	Group	15 (3)	3	31	32.5 (7.9)	7.5	10	2
				Light AE	Brisk walking (10 min); jogging (5 min); exercises in standing; sitting postures (20 min)				30	31.3 (7.9)		10	
Ho (2012)	China	Inpatient	SANS	MBE	Wu style tai chi with 22 simple movements	N/A	24 (12)	12	15	53.0 (N/A)	27.8	0	2
				TAU	Treatment as usual				15			0	
Ho (2016)	China	Inpatient	PANSS-N	MBE	Wu style tai chi with 22 simple movements	Group	48 (12)	12	51	52.4 (9.6)	29.9	0	2
				Moderate AE	15 min of warm up; stretching and joint movements (15 min); walking (10 min); stepping (10 min); mild weight training (10 min); cool down stretching (15 min)				51	55.0 (7.4)		1	
				TAU	Treatment as usual				51	54.7 (8.0)		3	
Ikai (2013)	Japan	Outpatient	PANSS-N	MBE	Warm up and loosening up exercises (14 min); yoga postures (28 min); deep relaxation (7 min); breathing exercises (8 min)	Group	8 (8)	8	25	54.8 (9.0)	26.1	3	6
				AC	Regular day care program (e.g. social skills training; psycho education)				24	51.5 (15.1)		2	
Ikai (2014)	Japan	Outpatient	PANSS-N	MBE	Warm up and loosening up exercises (14 min); yoga postures (28 min); deep relaxation (7 min); breathing exercises (8 min)	Group	8 (8)	8	25	53.5 (9.9)	25.0	7	4
				AC	Regular day-care program (e.g. social skills training; and psycho-education)				25	48.2 (12.3)		7	
Ikai (2017)	Japan	Inpatient	PANSS-N	MBE	Chair yoga: warm up and loosening up exercises (4 min); yoga postures (10 min); deep relaxation (3 min); breathing exercises (3 min)	N/A	24 (12)	12	28	55.5 (11.4)	26.2	3	6
				TAU	Treatment as usual				28	55.0 (15.8)		2	

(continued on next page)

Table 1 (*continued*)

Study	Country	Setting	Outcome Scale	Format	Intervention descriptions	Treatment delivery	No. of sessions (duration in weeks)	duration (weeks)	N	Mean age (SD)	Duration of illness (years)	Intervention drop-outs	RoB
Jayaram (2013)	India	Inpatient and outpatient	SANS	MBE	Loosening exercises (10 min); yoga postures (20 min); breathing exercises (18 min); relaxation (3 min)	N/A	N/A (4)	4	15	28.3 (4.7)	6.0	0	0
				TAU	Waiting list				28	29.5 (8.2)		16	
Kaltsatou (2015)	United States	Inpatient	PANSS-N	Moderate AE	Warm up (10 min); Greek traditional dancing (40 min); cooling down (10 min)	Group	104 (35)	35	16	59.5 (19.6)	34.4	0	5
				TAU	Treatment as usual				15	60.4 (8.6)		0	
Kang (2016)	China	Outpatient	PANSS-N	MBE	Wu-style Cheng form Tai chi Chuan with 22 simple movements combined with social skills training	Group	26 (52)	52	116	49.9 (12.1)	20.5	0	4
				TAU	Treatment as usual				126			0	
Kimhy (2015)	United States	N/A	SANS	Moderate AE	Warm-up (10 min); aerobic exercise using videogames, treadmill machines, a stationary bike and an elliptical machine (45 min); cool down (5 min)	Group	36 (12)	12	16	36.6 (10.4)	N/A	3	4
				TAU	Treatment as usual				17	37.2 (9.9)		4	
Lin (2015)	China	Outpatient	PANSS-N	MBE	Hatha yoga: breathing control (10 min); body postures (40-45 min); relaxation (5 min)	Group	36 (12)	12	48	23.8 (6.8)	2.3	3	4
				Moderate AE	Included walking on a treadmill (15-20 minutes); stationary cycling (25-30 minutes); cool down stretching (5 minutes)				46	24.6 (7.9)		6	
				TAU	Waiting list				46	25.3 (8.1)		7	
Loh (2016)	Malaysia	Inpatient	PANSS-N	light AE	Warm-up (5 min); walking exercise (20 min); cool down (5 min)	Group	39 (13)	13	52	21.6 (10.2)	20.3	4	3
				TAU	Treatment as usual				52			0	
Manjunath (2013)	India	Inpatient	PANSS-N	MBE	Loosening exercises (10 min); yoga postures (20 min); breathing exercises (18 min); relaxation (3 min)	Group	10 (2)	2	44	16.9 (8.2)	9.0	5	1
				Light AE	Brisk walking (10 min); jogging (5 min); exercises in standing and sitting postures (20 min)				44	17.1 (8.1)		1	
Oertel-Knöchel (2014)	Germany	Inpatient	PANSS-N	Moderate AE	Warm-up (10 min); boxing and circuit training (25 min); cool down (10 min)		12 (4)	4	8	44.6 (13.8)	10.3	N/A	3
				AC	Relaxing exercises	Group			11	34.9 (9.3)		N/A	
				TAU	Waiting list				10	38.3 (4.51)		N/A	
Paikkat (2015)	India	Inpatient	PANSS-N	MBE	Yoga: standing, lying and, sitting postures	Group	28 (4)	4	15	N/A	N/A	1	2
				TAU	Treatment as usual				15			1	
Pajonk (2010)	Germany	Outpatient	PANSS-N	Moderate AE	Cycling at a targeted heart rate	Group	36 (12)	12	13	34.8 (10.2)	10.45	0	3
				AC	Table Soccer				11	32.9 (10.6)		0	
Scheewe (2013)	The Netherlands	Outpatient (majority)	PANSS-N	Moderate AE	Cardio-vascular exercises combined with muscle strength exercises	Group	52 (26)	26	31	29.2 (7.2)	6.7	11	4
				AC	Occupational therapy				32	30.1 (7.7)		13	

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Setting	Outcome Scale	Format	Intervention descriptions	Treatment delivery	No. of sessions (duration in weeks)	duration (weeks)	N	Mean age (SD)	Duration of illness (years)	Intervention drop-outs	RoB
Su (2016)	Taiwan	Outpatient	PANSS-N	Moderate AE	Warming up by walking (5 min); treadmill exercise (30 min); cooling down (5 min)	Individual	50 (13)	13	30	37.6 (8.2)	13.0	0	4
				AC	Warm-up (3 min); flexibility: toning and balance exercises (25 min); cool down (2 min)				27	36.7 (8.3)		0	
Svatkova (2015)	The Netherlands	Outpatient (majority)	PANSS-N	Moderate AE	Aerobic exercise using bicycle, rowing machine, cross trainer and a treadmill machine (40 min); anaerobic exercise (20 min)	N/A	52 (26)	26	16	28.8 (7.4)	7.5	0	4
				AC	Occupational therapy				17	31.3 (8.2)		0	
Varamabally (2012)	India	Outpatient	PANSS-N	MBE	Loosening exercises (10 min); yoga postures (20 min); breathing exercises (18 min); relaxation (3 min)	N/A	25 (4)	4	47	18 (5.3)	9.8	39	1
				light AE	Brisk walking (10 min); jogging (5 min); exercises in standing and sitting postures (20 min)				37	16.1 (5.6)		22	
				TAU	Treatment as usual				36	15.7 (5.1)		34	
Visceglia (2011)	United States	Inpatient	PANSS-N	MBE	Yoga: breathing exercises, warm up, postures and relaxation	Group	16 (6)	6	10	37.4 (13.7)	N/A	0	2
				TAU	Waiting list				8	48.1 (11.2)		0	

PANSS-N = Positive And Negative Syndrome Scale- Negative subscale; SANS = Scale for the Assessment of Negative Symptoms; RoB = Risk of bias; AE = Aerobic exercise; MBE = Mind-body exercise; TAU = Treatment as usual; N/A = Not Available

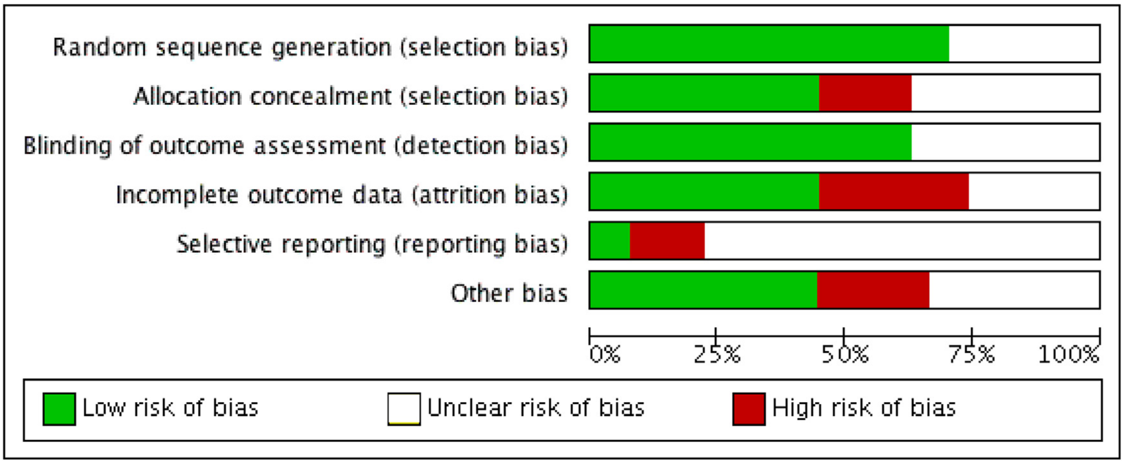

Fig. 2. Risk of bias across studies.

et al. (2015) and Lutgens et al. (2017) analyzed pre-post change scores instead of post scores only. Furthermore, Broderick et al. (2015, 2017) reported mean PANSS negative scores in contrast with the standardized effect size (Hedges' g) as used in this study.

The overall effect sizes varied across studies. Meta-analyses on negative symptoms of PE (Dauwan et al., 2015; Lutgens et al., 2017) found effect sizes of Hedges' $g = 0.49$ ($p < 0.000$) and pooled SMD = 0.36 (95% CI = −0.71, −0.01) respectively, compared to any control group. Despite a larger study pool and stricter inclusion criteria of studies in this meta-analysis the effect sizes are relatively similar. However, importantly different is the effect of AE versus AC. Where the meta-analysis of Dauwan et al. (2015) found an effect of Hedges' $g = 0.326$ ($p = 0.002$), this meta-analysis could not find a significant effect. Firth et al. (2015) only examined the effects of AE compared to any control group. An effect size of SMD = −0.44 (95% CI −0.78, −0.09, $I^2 = 0\%$) was found, which is slightly higher compared to our findings. Yoga compared to standard (Broderick et al., 2015) and non-standard care (Broderick et al., 2017) was significantly more effective in reducing mean PANSS scores with respectively 1.92 and 1.15 (range 7–49). The meta-analysis of Zheng et al. (2016) examining the effects of tai-chi, showed a large effect (SMD = 0.87, 95%CI = −1.15, −0.24). The difference in effect size with this meta-analysis can be explained by a larger study pool of tai chi studies available to Zheng et al. (2016) which were not available for this meta-analysis due to language restrictions (only studies in English were included). With regard to the heterogeneity, almost all studies found moderate to high heterogeneity, similar to our findings. Only the meta-analysis of Firth et al. (2015) had low heterogeneity (0%), but they only included five studies in their analysis. Light AE (e.g. walking and postures) served as an intervention condition in our meta-analysis, but not in other studies (Dauwan et al.,

Study name	Comparison	Statistics for each study						
		Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Bathia (2017)	LAE vs TAU	0,048	0,161	0,026	-0,268	0,365	0,298	0,766
Varamabally (2012)	LAE vs TAU	0,295	0,271	0,074	-0,237	0,826	1,087	0,277
Beebe (2005)	LAE vs TAU	3,499	0,976	0,952	1,586	5,411	3,586	0,000
Loh (2016)	LAE vs TAU	0,831	0,207	0,043	0,425	1,237	4,011	0,000
Total Light AE		0,672	0,343	0,118	-0,001	1,345	1,956	0,050
Bathia (2017)	MBE vs TAU	0,371	0,158	0,025	0,063	0,680	2,357	0,018
Ho (2016)	MBE vs TAU	-0,135	0,199	0,039	-0,525	0,254	-0,680	0,497
Lin (2015)	MBE vs TAU	1,039	0,251	0,063	0,548	1,531	4,141	0,000
Varamabally (2012)	MBE vs TAU	0,017	0,232	0,054	-0,438	0,472	0,075	0,940
Ho (2012)	MBE vs TAU	0,247	0,357	0,127	-0,452	0,946	0,692	0,489
Ikai (2013)	MBE vs AC	0,876	0,295	0,087	0,298	1,454	2,972	0,003
Ikai (2014)	MBE vs AC	0,129	0,279	0,078	-0,418	0,675	0,461	0,645
Ikai (2017)	MBE vs TAU	-0,303	0,277	0,077	-0,847	0,241	-1,092	0,275
Jayaram (2013)	MBE vs TAU	-0,396	0,379	0,144	-1,140	0,347	-1,045	0,296
Kang (2016)	MBE vs TAU	0,610	0,131	0,017	0,354	0,866	4,670	0,000
Paikkat (2015)	MBE vs TAU	2,710	0,516	0,266	1,700	3,721	5,257	0,000
Visceglia (2011)	MBE vs TAU	1,447	0,512	0,262	0,444	2,451	2,826	0,005
Total MBE		0,461	0,168	0,028	0,131	0,790	2,740	0,006
Ho (2016)	MAE vs TAU	-0,067	0,199	0,039	-0,456	0,322	-0,336	0,737
Lin (2015)	MAE vs TAU	0,706	0,255	0,065	0,207	1,205	2,770	0,006
Oertel-Knöchel	MAE vs TAU+AC	0,242	0,405	0,164	-0,552	1,036	0,597	0,551
Acil (2008)	MAE vs TAU	1,214	0,388	0,151	0,453	1,975	3,126	0,002
Kaltsatou (2015)	MAE vs TAU	0,051	0,350	0,123	-0,635	0,737	0,145	0,885
Kimhy (2015)	MAE vs TAU	0,250	0,381	0,145	-0,497	0,998	0,656	0,512
Pajonk (2010)	MAE vs AC	0,479	0,480	0,231	-0,462	1,420	0,997	0,319
Scheewe (2013)	MAE vs AC	-0,110	0,314	0,099	-0,725	0,506	-0,349	0,727
Su (2016)	MAE vs AC	0,182	0,297	0,088	-0,400	0,763	0,612	0,541
Svatkova (2015)	MAE vs AC	-0,216	0,341	0,116	-0,884	0,452	-0,633	0,527
Totaal Moderate AE		0,241	0,135	0,018	-0,023	0,505	1,790	0,074
Total PE		0,434	0,121	0,015	0,196	0,671	3,581	0,000

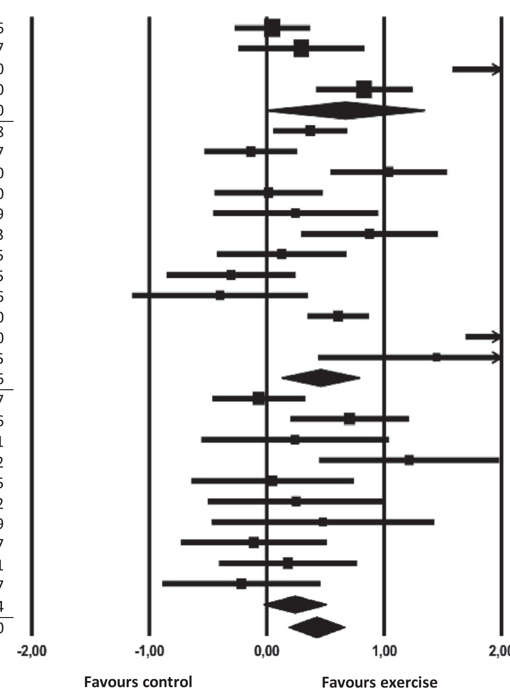

Fig. 3. Forest plot of the main analysis and subgroup analysis.
Intervention and control conditions in the overall analyses were pooled for studies with more than one intervention or control group in order to prevent double counting of subjects.
AE = Aerobic Exercise; LAE = Light Aerobic Exercise; MBE = Mind-Body Exercise; MAE = Moderate Aerobic Exercise; PE = Physical Exercise.

Table 2
Random effect sizes, heterogeneity and publication bias in the main, subgroup, sensitivity and, moderator analyses.

Analysis Intervention	Control	Random effect sizes Number of contrasts	Hedges' g	(95% CI)	Z	Heterogeneity p-value of Z	Q (df)	p-value of Q	I^2	Publication bias ($p < 0.05$)
1. All exercise	Any control	22	0.434	(0.196–0.671)	3.581	0.000	75.57	0.000	76/ HIGH	Yes
Subgroup analyses										
2. Mind-body exercise	Any control	12	0.461	(0.131–0.790)	2.740	0.006	57.90 (11)	0.000	81/ HIGH	Yes
3. Aerobic exercise	Any control	14	0.341	(0.079–0.604)	2.546	0.011	36.03 (13)	0.001	64/ MOD	No
4. Moderate AE	Any control	10	0.241	(−0.023–0.505)	1.790	0.074	15.55 (9)	0.077	42/ LOW	No
5. Light AE	Any control	4	0.672	(−0.001–1.345)	1.956	0.050	19.28 (3)	0.000	84/ HIGH	No
Sensitivity analyses										
1. All exercise	TAU	16	0.552	(0.253–0.850)	3.623	0.000	76.34 (15)	0.000	80/ HIGH	Yes
1. All exercise	Active control	7	0.171	(−0.138–0.479)	1.086	0.277	9.17 (6)	0.164	35/LOW	Yes
3. Aerobic exercise	TAU	10	0.499	(0.160–0.839)	2.881	0.004	25.11 (9)	0.014	52/ MOD	Yes
4. Moderate AE	TAU	6	0.433	(0.023–0.842)	2.072	0.038	12.72 (5)	0.026	61/ MOD	No
4. Moderate AE	Active control	5	−0.003	(−0.315–0.309)	−0.022	0.983	2.23 (4)	0.693	00/ NONE	Yes
2. Moderator analyses on mind-body exercise										
High quality studies		6	0.464	(0.139–0.789)	2.797	0.005	17.77 (5)	0.003	72/ MOD	No
Outliers removed $g > 2.0$		11	0.326	(0.046–0.607)	2.285	0.022	37.43 (10)	0.000	73/ MOD	No
≥ 36 sessions		5	0.317	(−0.228–0.862)	1.139	0.255	21.04 (4)	0.000	81/ HIGH	No
≥ 12 weeks exercise		5	0.303	(−0.168–0.774)	1.262	0.207	22.91 (4)	0.000	83/ HIGH	No
Outpatients		6	0.499	(0.221–0.777)	3.514	0.000	13.72 (5)	0.017	64/ MOD	No
Supervision		10	0.417	(0.061–0.773)	2.297	0.022	53.48 (9)	0.000	83/ HIGH	No
Group intervention		8	0.734	(0.332–1.137)	3.578	0.000	41.25 (7)	0.000	83/ HIGH	No
3. Moderator analyses on aerobic exercise										
High quality studies		5	0.162	(−0.184–0.509)	0.918	0.359	6.586 (4)	0.159	39/ LOW	Yes
Outliers removed $g > 2.0$		13	0.285	(0.060–0.511)	2.481	0.013	25.10 (12)	0.014	52/ MOD	No
≥ 36 sessions and/or ≥ 12 weeks		10	0.332	(−0.015–0.679)	1.877	0.060	28.07 (9)	0.001	68/ MOD	No
Outpatients		9	0.399	(0.030–0.768)	2.118	0.034	25.45 (8)	0.001	69/ MOD	No
Supervision		10	0.244	(0.010–0.478)	2.042	0.041	14.39 (9)	0.109	37/ LOW	No
Group intervention		11	0.425	(0.098–0.753)	2.544	0.011	33.56 (10)	0.000	70/ MOD	Yes

AE = Aerobic exercise; TAU = Treatment as usual; MOD = Moderate.

2015; Lutgens et al., 2017). Analyzing light AE as a control group might have negatively biased the effect of exercise in these meta-analyses. Furthermore, we excluded one of two articles (Behere et al., 2011; Varambally et al., 2012) from the same study to avoid bias in the effect size, whereas Dauwan et al. (2015) included both articles.

4.3. Heterogeneity and publication bias

Publication bias did not negatively influence the effect sizes. Furthermore, the heterogeneity of the offered interventions was moderate. Sensitivity and moderator analyses did not substantially lower the heterogeneity. The amount of heterogeneity warrants a careful interpretation of the results. Although our overall effect sizes suggest that PE interventions are moderately effective in reducing negative symptoms, not all included studies have found these effects and we have not been able to identify which underlying factors cause these variations in findings between different studies.

4.4. Intensity, number of sessions and duration

A systematic review (Stanton and Happell, 2014) about program variables for AE in people with schizophrenia recommended a frequency of exercising minimally three days a week for a period of twelve weeks. A meta regression analysis in our study on PE that included the number of sessions and the duration of training (in weeks) was not significant. Furthermore, former studies (Firth et al., 2016a; Stanton and Happell, 2014) recommended a moderate intensity for AE interventions. Subgroup analyses on moderate or light AE in our meta-analysis did not show significant effects. Therefore, recommendations for intensity, number of sessions or duration of PE cannot be made.

4.5. Group and supervision

Drop-out rates in some of the studies are high, likely due to motivational problems (Strauss et al., 2014) and sedentary behavior (Vancampfort et al., 2017), which is associated with negative symptomatology. It has been suggested that group interventions result in more compliance than interventions designed for individuals (Marzolini et al., 2009), which was also the case in our study. In addition, the presence of a supervisor was also suggested as a motivating factor (Firth et al., 2016b). However, in this study we could not find a correlation between drop-outs and the use of supervised interventions. In addition, moderator analyses on MBE and AE interventions with supervision did not result in a higher effect size. However, heterogeneity decreased in a meta-analysis on supervised AE interventions while the effect size remained significant (Hedges' $g = 0.24$, $I^2 = 37$, $Q = 33.6$ (df = 10), $p = 0.04$). Based on our findings, we recommend group delivered exercise interventions. The evidence for the use of a supervised intervention is not clear and should be further investigated in RCT's.

4.6. Strengths and limitations

A strength of this study is that it is the first meta-analysis that makes a distinction between PE interventions that focus on relaxation (MBE) and PE interventions that focus on exertion (AE). The study was conducted according to the PRISMA guidelines and was registered prior to the start of the search in accordance with the PROSPERO protocol, which is digitally accessible through the PROSPERO register. The main limitation is the high percentage of heterogeneity, which did not decrease even after several attempts with various sensitivity analyses. The heterogeneity could be explained by the high variety in treatment protocols. A second limitation is the poor methodological quality of most included studies. Furthermore, most studies on MBE interventions were conducted in Asian countries (e.g. China, India). This may limit applicability of the results in western populations. A final limitation to mention is that we were only able to make a crude difference between light and moderate AE interventions. A better distinction of exercise intensity might be based on intended metabolic effects, such as the maximum heartrate or maximal oxygen uptake (Norton et al., 2010).

However, mostly this information was not available. The overall methodological flaws and heterogeneity of the included studies impede strong conclusions on the effect of exercise to reduce negative symptoms.

4.7. Future research

The evidence of PE interventions, especially MBE interventions, showed promising effects. Furthermore, given the empirical evidence demonstrating beneficial effects of PE, it would be worthwhile to examine how PE is currently implemented in mental health care and how this could be improved. This was beyond the scope of the current review. The heterogeneity in MBE interventions necessitates the use of more standardized interventions. Also, clear descriptions of interventions increase the possibility of comparing exercise interventions in meta-analyses and may help to identify the causes of heterogeneity among different studies. We recommend the use of the Consensus on Exercise Reporting Template that is developed to standardize the reporting of exercise interventions (Slade et al., 2016). More high quality, sufficiently powered studies with multiple treatment arms (i.e. MBE, AE and TAU) will allow for direct comparisons in future meta-analyses.

4.8. General conclusions

PE interventions showed a significant effect on negative symptoms in schizophrenia compared to any control group, with a slightly larger effect of MBE interventions versus control groups than AE interventions versus control groups. The results should be interpreted with care due to the low methodological quality and moderate to high heterogeneity of the included studies.

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